III. Remarks

After entry of the amendment, claims 36-45, 50, 51, 59, 60, 64, 66, 68 and 79-118 are pending.

The dependency of claims 36, 39, 42, 43, 79, 80, and 81 has been corrected in view of the cancellation of claim 71 and the addition of claim 94.

Claim 41 has been editorially amended in response to the rejection under 35 USC § 112.

Claim 44 has been editorially amended to correct the spelling of "polypeptide."

Claim 66 has been amended and remains supported by the specification at, for example, page 54, line 16 to page 57, line 28.

Claims 71 and 72 have been canceled without prejudice as being directed to a non-elected invention.

New claims 85-116 have been added to the application and are supported by the original claims. Claim 88 is also supported by the specification at, for example, page 5, lines 15-17.

No issues of new matter should arise and entry of the amendment is respectfully requested.

IV. Information Disclosure Statement

Applicants respectfully request that the Examiner acknowledge the references cited on the Information Disclosure Statement filed concurrently herewith.

V. Change of Inventorship

Applicants respectfully request that the PTO acknowledge the change of inventorship of the present application pursuant to an Amendment under 37 CFR § 1.48(h) filed July 16, 2001. In the amendment, Tiansheng Wang and Stewart K. Richardson were deleted as inventors. After entry of the Amendment under 37 CFR § 1.48(h), the inventors of the claims in the present application are David S. Garvey, L. Gordon Letts and Sang William Tam.

VI. Rejection under 35 U.S.C. § 103(a)

Claims 50, 51, 59, 60, 64, 66, 68, 36-41 and 79-84 are rejected under 35 U.S.C. § 103 as obvious over [Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064) or Depui et al (WO 96/24375)] in combination with Stamler et al (U.S. Patent No. 5,380,758)].

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention. Applicants discuss the rejection below as it applies to (i) independent claims 50 and 64 and the claims dependent thereon; (ii) independent claim 59 and the claims dependent thereon; (iii) independent claim 66 and the claims dependent thereon; (iv) claim 51 and the claims dependent thereon; (v) independent claim 68 and the claims dependent thereon; and (vi) independent claim 71 and the claims dependent thereon.

A. Independent Claims 50 and 64 and The Claims Dependent Thereon

Claims 50 and 64 are reproduced below for the Examiner's convenience.

> 50. A method for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

> 64. A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor compound comprising administering to a patient in need thereof a therapeutically effective amount of at least one bismuth complex of at least one proton pump inhibitor compound and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Applicants respectfully submit that **none** of the cited references are relevant to the above-identified claims. None of the cited references disclose or suggest the claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor. Since none of the cited references disclose or suggest the claimed methods, the invention cannot be obvious over the cited references.

To the extent the Examiner is relying on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does not provide any motivation or suggestion to use S-nitrosothiols or any other NO donors to improve the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor. There is no evidence of record of any relationship between Stamler's method of relaxing gastrointestinal smooth muscle and the claimed methods for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

None of the cited references provide any motivation or suggestion to use compounds that donate, transfer or release nitric oxide, induce the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are a substrate for nitric oxide synthase to improve the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor.

In view of the above, Applicants respectfully submit that claims 50 and 64 and the claims dependent thereon are unobvious over the cited references and respectfully request that the rejection under § 103 of these claims be withdrawn.

B. Independent Claim 59 and The Claims Dependent Thereon

Claim 59 is reproduced below for the Examiner's convenience.

> 59. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

WO 97/25064 discloses formulations comprising a proton pump inhibitor in combination with a non-steroidal anti-inflammatory compound or an antacid formulation and their methods of use for treating and preventing gastrointestinal disorders caused by a non-steroidal anti-inflammatory compound (Depui at pages 1-4). Depui discloses NO-releasing non-steroidal anti-inflammatory compounds, i.e., a non-steroidal anti-inflammatory compound that has been chemically bonded to a NO-releasing group (Depui at page 13, line 2). The NO-releasing non-steroidal anti-inflammatory compounds described by Depui are pro-drugs that are metabolized to the active non-steroidal anti-inflammatory compounds.

Depui does not disclose or suggest the compounds of the present invention that donate, transfer or release nitric oxide, induce the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulate endogenous synthesis of nitric oxide or are substrates for nitric oxide synthase.

To the extent the Examiner is relying on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does not provide any motivation or suggestion to use S-nitrosothiols or any other NO donors to treat or prevent Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer. Moreover, there is no evidence of record of any relationship between Stamler's method of relaxing gastrointestinal smooth muscle and the claimed methods.

None of the cited references provide any motivation to combine a proton pump inhibitor with a NO donor to arrive at the presently claimed invention. In view thereof, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to

independent claim 59 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

C. Independent Claim 66 and The Claims Dependent Thereon

Claim 66 is reproduced below for the Examiner's convenience.

> 66. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor to a patient comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, and, optionally, at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor; wherein the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase and the at least one nonsteroidal antiinflammatory drug and/or selective COX-2 inhibitor are at least two different compounds.

Applicants respectfully traverse the rejection and respectfully submit that the cited references do not disclose or suggest the presently claimed invention.

Nohara and WO 96/24375 are wholly unrelated to the presently claimed methods, as neither reference discloses or suggests decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor.

To the extent the Examiner is relying on WO 97/25064, Applicants respectfully submit that WO 97/25064 does not disclose or suggest the presently claimed invention which requires administering a NO donor, *where the NO donor is different from the NSAID*. Accordingly, the teaching in WO 97/25064 at page 13, lines 1-4 does not disclose or suggest the presently claimed methods.

To the extent the Examiner is relying on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does

not provide any motivation or suggestion to decrease or reverse gastrointestinal toxicity or facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. Moreover, there is no evidence of record of any relationship between Stamler's method of relaxing gastrointestinal smooth muscle and the claimed methods.

In view of the above, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to independent claim 66 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn.

D. Independent Claim 68 and The Claims Dependent Thereon

Claim 68 is reproduced below for the Examiner's convenience.

> 68. A method for treating an infection caused by *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention.

Nohara and WO 97/25064 are wholly unrelated to the presently claimed methods of treating an infection caused by *H. pylori*. Accordingly, these references cannot render the presently claimed invention obvious under any circumstances.

To the extent the Examiner is relying on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does not provide any motivation or suggestion to treat an infection caused by *Helicobacter pylori*. Moreover, there is no evidence of record of any relationship between Stamler's method of relaxing gastrointestinal smooth muscle and the claimed methods of treating an infection caused by *H. pylori*.

In view thereof, Applicants respectfully submit that the claim 68 and the claims dependent thereon are unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

E. New Independent Claims 85, 87 and 89

New independent claims 85, 87 and 89 are set forth below for the Examiner's convenience.

> 85. A method for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor compound and at least one S-nitrosothiol.
>
> 87. A method for treating or preventing an ulcer in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor and at least one S-nitrosothiol.
>
> 89. A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one S-nitrosothiol.

Applicants respectfully submit that these newly presented claims and the claims dependent thereon are unobvious over the combination of cited references.

In particular, each of the claims requires the use of an S-nitrosothiol and none of the cited references disclose or suggest the use of an S-nitrosothiol to treat the presently claimed methods.

To the extent the Examiner would rely on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does not provide any motivation or suggestion to arrive at the claimed invention.

Applicants respectfully submit that these newly presented claims are in condition for allowance.

F. New Independent Claim 94

New independent claim 94 is set forth below for the Examiner's convenience.

> 94. A method for treating or preventing a gastrointestinal disorder selected from the group consisting of Crohn's disease, ulcerative colitis, a stress ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, and a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Applicants respectfully submit that none of the cited references disclose or suggest the use of at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase to treat or prevent a gastrointestinal disorder selected from the group consisting of Crohn's disease, ulcerative colitis, a stress ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, and a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

To the extent the Examiner would rely on Stamler, Applicants respectfully submit that Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** (Stamler at column 9, line 34 to column 10, line 62). Applicants respectfully submit that the presently claimed methods are unrelated to relaxing gastrointestinal smooth muscle, and that Stamler does not provide any motivation or suggestion to arrive at the claimed invention. There is no evidence of record that there is any relationship between relaxing gastrointestinal smooth muscle (as taught by Stamler) and the presently claimed methods.

To the extent the Examiner would rely on WO 97/25064 at page 13, lines 1-4, Applicants respectfully submit that WO 97/25064 does not disclose or suggest any of the presently claimed methods, i.e., Crohn's disease, ulcerative colitis, a stress ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, and a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia.

Applicants respectfully submit that this newly presented claim and the claims dependent thereon are in condition for allowance.

G. New Claims 101-118

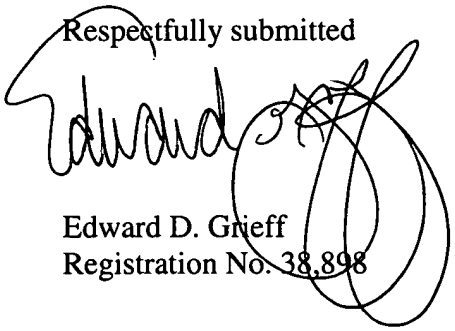
New claims 101-118 are directed to compositions and kits comprising at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof and (i) at least one S-nitrosothiol or (ii) at least one compound that induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. Applicants respectfully submit that none of the cited references disclose or suggest the claimed compositions or kits, and that these claims are in condition for allowance in view of the reasons discussed in detail in the preceding paragraphs.

VII. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 36-45, 50, 51, 59, 60, 64, 66, 68 and 79-118.

Examiner Rao is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application.

Respectfully submitted



Edward D. Grieff
Registration No. 38,898

Date: April 10, 2003
HALE and DORR LLP
1455 Pennsylvania Avenue, NW
Washington, DC 20004
Phone: (202) 942-8400